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(54) Title: BIOADHESIVE SOLID MINERAL OIL EMULSION

(57) Abstract

A viscous, film-forming, bioadhesive solid aqueous mineral oil emulsion ointment composition which is readily spreadable and adapted for topical application, which comprises water, mineral oil, an amount of a non-ionic surfactant effective to stabilize the emulsion, a polyethylene glycol, and a hydrophilic substituted cellulose and which optionally contains a pharmaceutically active agent, for example, a growth factor, e.g., TGFα, has wound healing promoting activity, particularly of wounds of the inside of the mouth.

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"BIOADHESIVE SOLID MINERAL OILEMULSION"

Field of the Invention

This invention relates to bioadhesive aqueous mineral oil emulsions, more particularly to viscous, film-forming, bioadhesive solid aqueous mineral oil emulsion ointment bases which are readily spreadable and adapted for topical application, to pharmaceutical compositions and products comprising them and to their use, e.g., in the healing of wounds.

Background of the Invention

Aqueous mineral oil emulsions have long been known and used in formulating topical cosmetic and pharmaceutical compositions. Generally speaking, bioadhesiveness, thereof, i.e., the ability of a thick coating thereof to adhere tenaciously to moist skin or a mucosal surface to which it is applied, is not a particularly important functional requirement. One end-use area in which bioadhesiveness is an important factor is pharmaceutical compositions which are applied to wounds to promote the healing thereof. Often, the fluid exudate from the wound tends to create a barrier between the therapeutic agent or agents in the medicament applied to the wound and the exposed surface area of the wound. Alternatively, the exudate will physically dislodge the medicament from the wound area, particularly in the inside of the mouth, where copious amounts of saliva usually are present. In

the case of a covered wound, the exudate can promote the absorption of the medicament into the wound covering and away from the surface of the wound.

As a class, aqueous mineral oil emulsions have poor bioadhesiveness and the more viscous the emulsions, the more likely it is to not form a bond to the surface of the wound, particularly when the wound is moist. This problem of non-adherence is particularly acute in the case of wounds, ulcers and lesions on the inside of the mouth. There saliva often prevents even initial adherence to the wound area or rapidly causes dislodgement of the medication from the wound area.

It has now been found that certain aqueous mineral oil emulsions can be rendered bioadhesive by the combination of a hydratable particulate cellulose derivative and a water-dispersible polymer which inhibits the hydration of the cellulose derivative prior to its application to the wound area. It has further been found that these novel aqueous mineral oil vehicles are excellent vehicles for wound-healing promoters, including growth factors such as TGFα.

Summary of the Invention

In one composition aspect, this invention relates to an ointment base adapted for cosmetic and pharmaceutical uses. This ointment is a viscous, bioadhesive solid aqueous mineral oil emulsion ointment composition adapted for topical application, comprising water, mineral oil, optionally an amount of a non-ionic surfactant effective to stabilize the emulsion, a polyalkylene glycol, and a hydrophilic substituted cellulose.

In another composition aspect, this invention relates to a pharmaceutical composition adapted for topical use comprising a mixture of an ointment base of this invention and a pharmaceutically active agent, e.g., TGFα.

In articles of manufacture aspects, this invention relates to dispensing containers containing the compositions of this invention and kits comprising same.

In a method aspect, this invention relates to a method of promoting the healing of a wound or lesion on the skin or mucosal surface which comprises applying to the affected area an amount of a composition of this invention effective to promote the healing thereof.

In a process aspect, this invention relates to methods for producing the compositions of this invention.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

Detailed Description of the Invention

The ointment base of this invention is a viscous, bioadhesive, solid aqueous mineral oil emulsion adapted for topical use which comprises mineral oil; water; an amount of a water-dispersible particulate hydrophilic substituted cellulose dispersed in the aqueous phase of the emulsion effective to produce, when the emulsion is spread on a moist skin or mucosal surface, a stable, coherent layer which resists removal therefrom by water or a body fluid associated therewith; an amount of a water-soluble polyethylene glycol dissolved in the aqueous phase of the emulsion effective to reduce the water activity of the emulsion sufficiently to retain the substituted cellulose therein in particulate, non-fully hydrated form and to increase the viscosity thereof to a spreadable viscous paste; and optionally an amount of a non-ionic surfactant effective to render the emulsion storage-stable.

The ointment base of this invention is characterized by being highly bioadhesive. The term "bioadhesive" as used herein means that a film or layer of ointment applied to moist skin or a mucosal surface persistently

adheres thereto with an adhesive bond which is at least as strong as the internal cohesive strength of the ointment. The effect of this bioadhesive property is that a film or layer thereof resists being physically wiped off the skin or mucosal surface to which it is applied or being washed off with a body fluid associated with a mucosal surface to which it is applied. This is particularly important in the case of oral mucosa because the tongue tends to physically remove the film or layer.

The ointment base is a viscous solid at use temperatures which ordinarily are at or near body temperature. Although the physical properties are temperature-dependent, at use temperatures, it typically has a viscosity of at least 10,000, preferably at least 15,000, and more preferably at least 19,000 centipoise. Although highly viscous, it is readily spreadable on the skin and mucosal areas and is adapted for topical use. Desirably, it is dispensable by extrusion from a toothpaste or ointment tube-type container, but may also be dispensed in capsules or in jars. When spread on the skin or a mucosal surface, or a wound, lesion or ulcer therein, it forms a continuous layer which adheres strongly and persistently thereto and which resists removal therefrom by physical means or by the body fluid associated with a mucosal surface, e.g., saliva. The film or layer forms a tenacious barrier to the atmosphere which promotes healing and preferential diffusion of pharmaceutically active ingredients into the wound tissue rather than into mucosal fluids.

The mineral oil employed in the compositions of this invention is preferably pharmaceutical grade. The mineral oil is employed in an amount which produces an ointment base having the desired physical properties, e.g., from about 20-45%, preferably about 24-41%, and most preferably about 28-37%, e.g., about 33%. The amount of mineral oil and/or of the polyalkylene glycol employed is

adjusted to provide the desired end use viscosity of the ointment base of this invention.

The ointment base contains dispersed therein in particulate form a hydrophilic substituted cellulose, i.e., a cellulose derivative which when hydrated with water forms a tacky or sticky sol or gel. A wide variety of such cellulose derivatives are well known in the art, e.g., those substituted by one or more hydrophilizing groups, e.g., carboxyalkyl and hydroxyalkyl. Preferred are those having both hydroxyalkyl and alkyl groups, i.e., a hydroxyalkyl$_A$-alkyl$_B$cellulose, preferably wherein alkyl$_B$ is methyl or alkyl$_A$ is propyl, and most preferably a hydroxypropyl$_A$-methyl$_B$cellulose.

By being present in the ointment base in suspended particulate form, rather than in hydrated sol or gel form, the substituted cellulose renders the vehicle bioadhesive, a property not possessed by aqueous mineral oil emulsion ointments generally. The particle size of the substituted cellulose can vary substantially, e.g., from about 20 microns to about 400 microns. The pharmaceutical grades of these products which are available commercially generally fall within this size range.

The substituted cellulose is usually present in the ointment base in an amount from about 5% to 45%, preferably about 22% to 35%, e.g., about 29%.

The polyalkylene glycol is employed in an amount effective to stabilize the emulsion and prevent its separation upon storage. Such an amount will usually increase the final viscosity of the ointment base substantially, e.g., to at least 11,000 centipoise. It will also decrease substantially the water activity of the ointment base, i.e., prevent the water in the ointment base from swelling the hydrophilic cellulose derivative present therein and thereby destroy its non-fully hydrated particulate form and its ability to render the vehicle bioadhesive. From about 20% to about 55%, pref-

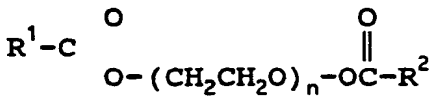
erably about 27% to about 45 wt.%, and most preferably about 35% to about 40%, e.g., about 37%, on a 100% solids per volume basis is ordinarily employed. These ranges translate to about 41-71%, preferably about 51-66%, e.g., about 61% (on a v/v basis) for a 35% aqueous solution.

The polyalkylene glycol can vary substantially in molecular weight, provided it is hydrophilic enough to be dispersible in water and thereby reduce the water activity of the water in the ointment base. The polyethylene glycols having a molecular weight in the range of 400 to 11,000, e.g., 7,000 to 9,000, are preferred. PEG 8000 is especially preferred.

As would be apparent to those skilled in the pharmacy art, since the PEG is only one member of a known class of α-hydro-ω-hydroxy-polyoxyalkylenes, e.g., of the formula $H[O\text{-alkylene}]_m\text{-}[O\text{-alkylene}]_n\text{-}OH$ wherein the alkylene monomeric units can be the same or different, e.g., ethylene-1,2- and 1-3-propylene and m and n are positive integers. The PEG can contain other monomeric units besides oxyalkylene in the molecule and/or its terminal hydroxy groups can be modified, provided the aforesaid physical properties are not adversely affected. Also, other hydrophilic polymeric equivalents of the PEG polymers can be employed. Therefore, contemplated equivalents of the compositions of this invention are those wherein the PEG component thereof is replaced partially or wholly by one of these functionally equivalent hydrophilic polymers.

The emulsion is optionally also further stabilized with a non-ionic surfactant, of which many are known in the art and used to produce stable aqueous emulsions in the cosmetic and pharmacy fields. See, e.g., Schwartz et al., "Surface Active Agents and Detergents," Vol. II, pp. 120-143 (Interscience Pub. Inc., N.Y., 1958). A preferred class of non-ionic surfactants are the polyoxyethylene surfactants (ethoxylates) in which a polyoxy-

ethylene block polymer chain is terminated with a less soluble group, e.g., an alkylphenol ether group, an alcohol or mercaptan ether group, an amide group, or a carboxylic acid ester group, e.g., a surfactant of the formula



wherein n is between 5 and 25 and R^1 and R^2 each is a fatty acid chain of between 15 and 25 carbon atoms. The polyoxyethylene sorbitans, e.g., the Tweens, are a well known class of ethoxylate esters of a mixture of anhydro-sorbitols. Tween 80 is a preferred example of this class.

The surfactant when present is usually employed in the range of from about 0.01 to about 3%, preferably about 0.05 to 1.5%, e.g., about 0.7%.

In one embodiment, the emulsion compositions of this invention comprise a pharmaceutically active (therapeutic) agent, which can be a local anesthetic, e.g., benzocaine or xylocaine, and/or a compound known to promote the healing of wounds, e.g., a bacteriostat or bacteriocide, e.g., chloroxylenol or povidone-iodide, a sulfa drug, an antibiotic, fungistat or fungicide, e.g., tetracycline, nystatin or neomycin, an anti-inflammatory agent, e.g., zinc oxide and/or a steroid such as hydrocortisone, prednisolone, triamcinolone acetonide, halo-besterol propionate or beta-methasone dipropionate and/or a debriding agent, e.g., a proteolytic enzyme or biphen-amine hydrochloride (U.S. 4,497,824), chemotherapeutic agents (when the composition is used to treat skin cancer, e.g., melanoma) e.g., fluorouracil, and growth factors, e.g., epidermal growth factors (EGF), nerve GF, transforming GF, various colony stimulating factors (CSF), granulocyte/macrophage (G/M CSF), the interferons,

the cytokines, such as the int rleukins, e.g., lymphokines, ammonokines and the like. In a preferred such embodiment, the pharmaceutically active agent is TGF, more particularly TGFα, growth factor. For the preparation thereof, see, e.g., U. S. Patents 4,816,561, 4,863,899 and 4,874,746.

The ointment of this invention can be employed to promote the healing of a variety of abnormal conditions of the skin and mucosal membranes, e.g., wounds, ulcers and lesions associated with infected or traumatic wounds; thermal, electrical, chemical and traumatic burns; scrapes, abrasions; lesions associated with the urogenital tract; the tongue, the inside of the mouth or gingiva, the face, eye, nose, sinus, bacterial and fungal infections, especially those which produce lesions; athlete's foot which produces fissures or lesions in the skin; plantar warts; varicose ulcers; leg ulcers from impaired circulation; hemorrhoids and fissures in the colon; oral surgery; pimples, pustules or infected areas produced by splinters or other foreign bodies; bladder inflammations; senile keratosis; human, animal and insect bites; and any other wound, whether benign or malignant, sterile or infected with bacteria, virus or fungus, and psorasis, seborrhea, pururitis, pigmentatious abnormalities and skin cancer, particularly when it contains a chemotherapeutic agent.

The ointment compositions of this invention are particularly suited for the treatment of oral mucositis, which is a condition which frequently accompanies radiation or chemotherapy. A mucous membrane typically is formed of fast-growing cells which divide quickly and, like cancerous cells, tend to be killed by the therapy treatments. As a result, lesions in the mucous membrane often arise, for which an effective treatment has not heretofore been developed. Therefore, in a preferred aspect, this invention is directed to the treatment of

oral mucositis, particularly when associated with cancer therapy.

To treat a wound or ulcerated area of the skin or a mucosal surface, e.g., the inside of the mouth, the ointment base of this invention, alone (because the ointment base alone has wound healing promoting activity) or in admixture with a pharmaceutically active (therapeutic agent), e.g., is applied topically, preferably on successive occasions, e.g., as frequently as every hour or as infrequently as daily or longer, depending on the severity and intractability of the pathological condition. It is desirable to apply the ointment base mixture, promptly after the wound, lesion or ulcer appears or is inflicted and on successive occasions thereafter, e.g., once every 2-12 hours for 2-14 days or until the wound, lesion or ulcer is healed. Because the ointment base is film-forming and forms a coating over the wound, lesion or ulcer which acts as a barrier to the atmosphere and sources of further irritation and/or infection, it has a healing promoting effect, even in the absence of a pharmaceutically active agent therein. For the same reason, both forms can be used to promote the healing of internal wounds, e.g., stomach ulcers.

The ointment of this invention can also be used topically to ameliorate pain not associated with a wound, ulcer or lesion, e.g., a bruised area of the skin, in which case an anti-inflammatory agent, skin penetrant and/or local anesthetic is desirably present therein.

The amounts of the ointment base or a mixture thereof comprising one or more therapeutic agents applied to the affected area will depend on such factors as the degree or localization thereof, the concentration of therapeutic agent therein, the individual's responsiveness to the therapy and the amounts thereof required to cover the affected area. Generally, enough to provide a coating about 1-6 mm thick per application is effective.

The effectiveness of successively greater or smaller dosag s can determine the optimum effective individual dose.

Because of the heat labile nature of some pharmaceutically active agents and most biologics, including TGFα, they are advantageously sterile mixed with previously sterilized ointment base, since post-sterilization by gamma radiation tends to reduce the viscosity of the sterilized product to an unacceptably low level. The ointment base can be sterilized in a conventional manner, e.g., at 110°-125° for 10-30 minutes, e.g., in an autoclave.

The sterile ointment base can be sterile filled in a conventional manner into jars or ointment collapsible dispensing tubes and thereafter autoclaved and thereafter sealed therein or post-sterilized after filling. Ointments are sterile mixed with the therapeutic agent, e.g., TGFα, and thereafter sterile filled into the desired dispensing container.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and except where indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications cited herein are hereby incorporated by reference.

EXAMPLES

Example 1: Ointment Base

Dissolve 35 gm polyethylene glycol-8000 (Dow Chemicals, Inc.) in distilled water and bring the final volume to 100 ml. Add 0.45 g of Tween 80 to the thus-produced 35% (w/v) PEG 8000 solution and completely dissolve therein at 80°C. Mix 19.36 g mineral oil with Tween 80 and PEG-8000 mixture in a Polytron homogenizer until a milk-white emulsion is formed. Add 17 g hydroxypropylmethyl cellulose (HPMC, Dow Chemicals, Inc.) to the emulsion in the Polytron homogenizer with vigorous mixing. The resulting ointment base (hereinafter referred to by the arbitrary designation "TJ" and "TJ formulation") has the following composition.

Mineral Oil	33.3%
Tween 80	0.7%
PEG-8000 (35% wt/v in H_2O)	36.7%
HPMC	29.3%

Example 2: Sterile TGFα Ointment

Sterilize 5 g of the ointment base of Example 1 in a 20 ml glass vial by autoclaving at 121°C for 15 min. Under sterile conditions, cool to 4°C and add thereto an amount of TGFα appropriate for the intended end use, typically a submilligram amount per milliliter, e.g., 25 μg TGFα/0.25 ml of ointment base, and mix thoroughly. Sterile bottom fill into a 5 cc capped ointment dispensing tube. Crimp close the bottom of the filled tube in the conventional manner.

The thus-prepared TGFα ointments have highly desirable properties, including (1) bioadherence to oral mucous membrane; (2) sustained release of the excellent TGFα therefrom; (3) comfortable administration thereof to an ulceration wound; (4) complete in situ release of the TGFα therefrom; (5) autoclave sterilizability of the ointment base; and (6) retention of the TGFα therein in a bioactive form.

The TGFα-containing vehicle of Example 2 (TJ formulation) was subjected, both in vitro and in vivo, to evaluation to meet the therapeutical requirements for oral mucosities. The in vitro evaluation included TGFα release and extraction from the vehicle, autoclave sterilizability and the bioactivity and stability of TGFα in the formulation. The in vivo evaluation included TGFα uptake and tissue distribution of absorbed TGFα from hamster's cheek pouch.

The in vitro extractability of the TGFα from the TJ vehicle was determined both by exhaustive extraction of the mineral oil from the vehicle followed by reverse phase HPLC analysis of the extracted TGFα and by extraction at one-hour intervals of successive aliquots of PBS buffer of a 5:1 mixture of TGFα and C-14 labeled TGFα and measuring the radioisotope levels of the successive PBS buffer extracts.

The following are the results of the latter determination.

Release Rate of TGFα Released from TJ Formulation

	TJA-1	TJA-2	TJA-3	$\bar{X}$	S
0 hrs.	10%	6%	10%	8.6%	2.3
1 hr.	36%	33%	36%	35%	1.7
2 hrs.	49%	50%	51%	50%	1.0
3 hrs.	63%	56%	59%	59%	3.5
5 hrs.	70%	78%	82%	76%	6.1
7 hrs.	78%	90%	87%	85%	6.2

	TJ-1	TJ-2	TJ-3	$\bar{X}$	S
0 hrs.	8%	6%	6%	6.6%	1.1
1 hr.	31%	29%	31%	30%	1.1
2 hrs.	39%	38%	42%	39%	2.0
3 hrs.	48%	46%	48%	47%	1.1
5 hrs.	63%	60%	64%	62%	2.0
7 hrs.	72%	71%	71%	71%	0.5

TJA-1, TJA-2 and TJA-3: autoclaved formulations
TJ-1, TJ-2 and TJ-3: non-autoclaved TJ formulations

The storage stability of the TGFα in the TJ vehicle was determined at room temperature and at 4°C after 48 hours and after 4 days by extracting the TGFα after the test in PBS buffer and test for residual bioactivity by conventional membrane radioreceptor assay. The results of these bioactivity and stability studies are as follows:

(i) Bioactivity:

	TJ, autoclave	TJ, no autoclave
MRRA	86%	60%

(ii) Stability

	48 hrs. Room Temp.	48 hrs. 4°C	8th day 4°C	8th day Room Temp.
MRRA	51%	67%	56%	39%

The in vivo uptake of TGFα from the TJ vehicle was determined in Golden Syrian hamsters, female, approximately 150 gm using an ^{125}I-TGFα formulation (specific activity-45 μci/μg), the hamster's cheek pouch having a mechanically created wound. A pharmacokinetic study of tissue distribution of TGFα absorbed by the hamsters was also conducted. The methods employed were as follows:

1. Fast hamsters overnight.

2. Anesthetize hamsters by I.M. injection of ketamine HCl.

3. Create a 2 mm diameter wound on the right-hand side of hamster's cheek pouch by a biopsy punch.

4. Following the removal of the debridement and blood clot, administer 20 μl TJ formulation containing 26 μci 125I-TGFα onto the wound area by a Gilson Microman.

5. Keep the hamsters in their cages and give no water or food during the course of 6 hours study.

6. Select three hamsters at time 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours and 6 hours and select

one hamster at 24 hours for TGFα uptake and tissue distribution study.

7. Punch a needle into the hamster's heart and withdrawn 1 ml blood by a 5 ml syringe.

8. Sacrifice hamster by inhalation of an overdose of carbon dioxide vapor from dry ice in a closed chamber.

9. Immediately after sacrificing, remove the liver, kidney, thyroid, submaxillary gland, esophagus, stomach, small intestine, cecum, colon, 25 cm^2 skin on back, tongue and right-hand side of cheek pouch.

10. Flush the contents of esophagus, stomach, small intestine and cecum with water and collect the contents separately into a test tube.

11. Count the CPM of ^{125}I-TGFα that distributed in the hamster's tissue and GI contents.

The results of such a tissue distribution study are shown in the tables which follow.

I. Distribution of ^{125}I-TGFα in the Tissues

	15 min.	0.5 hrs.	1 hr.	2 hrs.	4 hrs.	6 hrs.	24 hrs.
Blood	0.01%	0.02%	0.04%	0.05%	0.13%	0.13%	0.22%
Liver	0.03%	0.07%	0.09%	0.17%	0.26%	0.24%	0.59%
Kidney	0.02%	0.07%	0.07%	0.14%	0.23%	0.27%	0.24%
Thyroid	0.005%	0.02%	0.02%	0.14%	0.39%	0.88%	2.84%
Submaxillary Gland	0.02%	0.05%	0.04%	0.20%	0.42%	0.77%	0.77%
Esophagus	0.001%	0.01%	0.01%	0.01%	0.26%	0.27%	0.04%
Stomach	0.01%	0.03%	0.05%	0.10%	0.74%	1.06%	1.23%
Small Intestine	0.01%	0.05%	0.04%	0.07%	0.12%	0.15%	0.40%
Cecum	0.003%	0.01%	0.02%	0.06%	0.04%	0.08%	0.05%
Colon	0.01%	0.02%	0.04%	0.06%	0.13%	0.12%	1.57%
Skin	0.04%	0.06%	0.03%	0.10%	0.14%	0.13%	0.13%
Tongue	0.85%	3.13%	4.82%	3.57%	3.37%	1.25%	0.66%
Cheek Pouch	76%	30%	70%	74%	74%	84%	21%

II. Distribution of ^{125}I-TGFα in the GI Cont nts

	15 min.	0.5 hrs.	1 hr.	2 hrs.	4 hrs.	6 hrs.	24 hrs.
Esophagus	0.00005%	0.01%	0.002%	0.01%	0.37%	0.27%	0.01%
Stomach	0.03%	0.056%	0.20%	0.40%	4.1%	7.8%	5.5%
Small Intestine	0.003%	0.01%	0.02%	0.02%	0.06%	0.05%	0.52%
Cecum	0.003%	0.01%	0.02%	0.02%	0.04%	0.05%	2.63%

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A viscous, film-forming, bioadhesive solid aqueous mineral oil emulsion ointment composition which is readily spreadable and adapted for topical application and which, when spread on a moist skin or mucosal surface, forms a stable, coherent layer thereon which resists removal therefrom by water or a body fluid associated with the surface to which it is applied, comprising water, mineral oil, an amount of a polyalkylene glycol and optionally a non-ionic surfactant effective to stabilize the emulsion, and a hydrophilic substituted cellulose.

2. A composition of claim 1, wherein the polyalkylene glycol is a polyethylene glycol having a molecular weight in the range of about 400 to about 11,000 D.

3. A composition of claim 2, wherein the polyethylene glycol is PEG 8000.

4. A composition of claim 1, wherein the substituted cellulose is a hydroxyalkyl$_A$-alkyl$_B$cellulose.

5. A composition of claim 4, wherein the hydroxyalkyl$_A$-alkyl$_b$cellulose is a hydroxypropyl-methylcellulose.

6. A composition of claim 1, wherein the mineral oil content is from about 20% to 45%, the substituted cellulose is present in an amount from about 50% to about

45%, the polyalkylene glycol cont nt is from about 20% to 55% and the composition contains from about 0.01 to about 3% of a non-ionic surfactant.

7. A composition of claim 1, wherein the mineral oil content thereof is about 24% to about 41%.

8. A composition of claim 1, wherein the mineral oil content thereof is about 33%.

9. A composition of claim 1, wherein the polyalkylene glycol content thereof is about 20% to about 50%.

10. A composition of claim 9, wherein the polyalkylene glycol content thereof is about 27% to about 45%.

11. A composition of claim 10, wherein the polyalkylene glycol content thereof is about 37%.

12. A composition of claim 1, wherein the substituted cellulose content hereof is about 5% to about 34%.

13. A composition of claim 12, wherein the substituted cellulose content thereof is about 35%.

14. A composition of claim 1, comprising about 0.05% to about 1.5% of the surfactant.

15. A composition of claim 1, having a viscosity of at least 10,000 centipoise.

16. A composition of claim 1, having a viscosity of at least 19,000 centipoise.

17. A composition of claim 1, comprising about 21% to about 41% of the mineral oil; about 20% to 50% of the

polyethylene glycol and about 22% to about 35% of the substituted cellulose and having a viscosity of at least 10,000 centipoise.

18. A composition of claim 1, comprising about 22% of the mineral oil, about 61% PEG 8000; about 17% of hydroxypropylmethylcellulose; about 0.05 to about 0.8% (v/v) of a polyoxyethylene sorbitan non-ionic surfactant; and having a viscosity of at least about 19,000 centipoise.

19. A composition of claim 1, as a homogenous mixture.

20. A composition of claim 1, additionally comprising at least one pharmaceutically active agent.

21. A composition of claim 19, comprising a local anesthetic.

22. A composition of claim 19, comprising TGFα.

23. A method of promoting the healing of a wound, ulcer or lesion on the skin or mucosal surface, comprising applying to the affected area an amount of a composition of claim 1 effective to promote the healing thereof.

24. A method of promoting the healing of a wound, ulcer or lesion on the skin or mucosal surface, comprising applying to the affected area an amount of a composition of claim 20 effective to promote the healing thereof.

25. A method of promoting the healing of a wound, ulcer or lesion on the skin or mucosal surface, comprising applying to the affected area an amount of a composi-

tion of claim 22 effective to promote the healing thereof.

26. A method according to claim 25, wherein the affected area is the inside of the mouth.

27. A method according to claim 25, wherein the composition is applied to the affected area on successive occasions.

28. A method according to claim 25, wherein the composition is applied to the affected area at least once a day on a plurality of successive days.

29. A method of promoting the healing of a wound, ulcer or lesion on the skin or mucosal surface which comprises applying to the affected area an amount of a composition of claim 1 containing a wound healing promoting amount of TGFα.

30. A method according to claim 29, wherein the affected area is the inside of the mouth and the composition is applied to the affected area at least once a day on a plurality of successive days.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/03812

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 9/107; 37/43
US CL :424/401; 514/939, 941, 969
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/401 434, 436, DIG. 13; 514/939, 941, 969

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,818,105 (COOPERSMITH) 18 JUNE 1974, column 2, lines 57-60 and column 4, Example 3.	1-20, 22-30
Y	US, A, 4,393,061 (YU) 12 JULY 1983, column 1, line 43 and lines 48-52.	21
Y	US, A, 4,867,970 (NEWSHAM) 19 SEPTEMBER 1989, column 2, lines 33-34 and lines 56-68, column 3, line 64, column 4, lines 37-58, and column 6, Table I and Examples 1 and 2.	1-20, 22-30
Y	US, A, 4,929,422 (POWELL) 29 MAY 1990, Abstract, column 7, lines 33 and 57, and claim 7.	1-20, 22-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be part of particular relevance
"E" earlier document published on or after the international filing date
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 JUNE 1993	20 AUG 1993
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